

## REMARKS

Claims 87, 89-98 are pending in the instant application.

No new matter has been added by this amendment.

### **Double Patenting**

Claims 87-96 have been rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-5 of US Patent No. 5,480,772. In response, Applicant submits herewith a terminal disclaimer along with the appropriate fee. Thus, this rejection has been overcome and should be withdrawn.

Claims 87-96 have also been rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-14 of US Patent No. 5,651,992. In response, Applicant submits herewith a terminal disclaimer along with the appropriate fee. Thus, this rejection has been overcome and should be withdrawn.

Claims 87-96 have also been rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-29 of US Patent No. 5,773,217. In response, Applicant submits herewith a terminal disclaimer along with the appropriate fee. Thus, this rejection has been overcome and should be withdrawn.

Claims 87-96 have also been rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-6 of US Patent No. 6,753,457. In response, Applicant submits herewith a terminal disclaimer along with the appropriate fee. Thus, this rejection has been overcome and should be withdrawn.

Claims 87-96 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-8 of copending Application No. 10/969,646. Applicant will submit a terminal disclaimer upon notice of allowable subject matter.

**Claim Rejection--35 U.S.C. § 112, first paragraph**

Claims 97 and 98 have been rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. According to the Examiner, “at the time of filing the art recognized that nuclear transfer or cloning to produce a term animal was unpredictable and pregnancy does not necessarily mean live births.” (See Office Action at page 3). Thus, the Examiner concludes that a skilled artisan would need to engage in a due amount of experimentation without a predictable degree of success to implement the invention as presently claimed. (See Office Action at page 5). Applicant traverses. Applicant submits that the unpredictability/inefficiency of maintaining pregnancy is inherent to most if not all cloning methods and outside the scope of the disclosed invention (See Lewis, R., The Scientist, (2005) 19(8):13-15, Appendix G). The level of efficiency of the methods invention is analogous to other methods, e.g., pronuclear injection, used in the art. (See Ebert, K.M., Schindler, J.E.S. Theriogenology, (1993)39:121-134, Tables 1, 3 and 4, Appendix A).

The claimed invention has revolutionized the field by increasing the efficiency of the process by solving problems associated with nuclear reprogramming that hindered earlier approaches. The development of reconstructed embryos may be influenced by many factors, including quality of the recipient oocyte, method of activation, and culture methods. (See Campbell, K., J. Anat. (2002) 200:267-275, Appendix B). Similarly, induction and maintenance of pregnancy may also be dependent upon a range of factors influenced both by the quality of the transferred embryo and the age, seasonality, nutritional and hormonal status of the surrogate recipient. (See Campbell at page 271, column 2). While it is possible to overcome the above mentioned variables out undue experimentation, published reports after the filing date overwhelmingly confirm that it is the use of an MII cytoplasm or unactivated egg cytoplasm that is required for reliable and successful reprogramming for cloning purposes. (See, specification at page 25, lines 21-26).

At the time of filing, the art taught that the production of whole cloned animals was possible from totipotent (embryonic nuclei) and also demonstrated the inefficiency of the nuclear transfer technique. (See McGrath, J., Solter, D., Science (1983) 220(4603):1300-2, Appendix C). The art, however, did not teach the ability to produce a cloned animal from somatic cell nuclei. The crucial and enabling technology for cloning whole animals was provided by the

present invention, i.e., the incubation of a nucleus in the cytoplasm of an oocyte at MII followed by contacting the nucleus with the cytoplasm of an activated egg. According to Campbell, in mammalian species, enucleated MII oocytes (unfertilized eggs) have now become the recipient cell of choice. (See Campbell at page 269, column 1).

According to the Examiner, the references Bourc'his, Fairburn and Hill state that reprogramming is the root cause of the inefficiency in nuclear transfer and inefficiency is equated with unpredictability. (See Office Action at page 4). Bourc'his, however, states that new information will clarify the causes and the extension of the observed variability or inefficiency seen in cloned embryos. (See Bourc'his at page 1545, column 1). Moreover, Hou et al., which demonstrated that DNA methylation reprogramming in bovine embryos is also affected by in vitro maturation, fertilization, and culture. (See Hou, J., et al. Sci. China C. Life Sci. (2007) 50(8):56-61, Appendix D). Although many of these factors may influence efficiency, Applicant submits that the level of efficiency or unpredictability associated with the claimed methods is well within the range of acceptable to those practicing in the art of the invention.

The invention is based on the ground-breaking discovery that reprogramming occurs by contacting a nucleus with the MII oocyte cytoplasm and an activated egg cytoplasm. Moreover, the method of Bourc'his is to study methylation, which only visualizes the heterochromatin (inactive) and interspersed repeated regions rather than the active gene regions. (See Bourc'his at page 1545, column 1). Furthermore, the expression pattern of any genes known to be involved in embryological development were not analyzed and euchromatic methylation patterns before implantation were similar in normal and cloned embryos, which represent the active gene regions. *Id.*

The Fairburn reference also makes the inference that inefficient reprogramming may be partly responsible for the low birth rates and developmental abnormalities, not the reprogramming, that often result from nuclear transfer. (See Fairburn at page R68, column 2). Fairburn also states that any data derived from any of the methylation studies is lacking direct evidence that aberrant DNA methylation patterns actually cause aberrant gene transcription patterns in cloned embryos. (See Fairburn at R70, column 1).

The Hill reference infers that gestational and neonatal abnormalities are consistent with irregular expression and likely incomplete reprogramming of imprinted genes; however, the reference does not have any direct evidence to support the inference. (See Hill at page 174). Additionally, Hill further infers that lack of normal *in utero* development is important to improving NT efficiency, and the cause appears to lie in the nuclear reprogramming process following NT, the NT technique itself, and epigenetic damage from embryos culture conditions. (See Hill at page 176). Corcoran et al., provides further evidence that the culture conditions alone can cause changes in the expression profile of genes known to be involved in development. (See Corcoran, D., et al., Mol. Reprod. Dev. (2007) 74(8):972-7, Appendix E). Again, the efficiency or level of unpredictability associated with the claimed methods are well within the range of acceptable to those practicing in the art of the invention.

The present claims require a cytoplasm of a MII oocyte and an activating egg cytoplasm. The teaching of extracts in the specification represent exemplary uses of MII oocyte cytoplasm and an activating egg cytoplasm. Applicant identified these compositions as reprogramming tools, and others have now confirmed the success of use of those tools either in the form of extracts or an enucleated oocyte, i.e., MII oocyte cytoplasm. (See, e.g., Sullivan, E.J., et al., Biol. of Rep. (2003) 70:146-153, Appendix H). Sullivan used a reprogramming extract from metaphase human cells as opposed to *Xenopus* or bovine oocytes. *Id.* The process for making the activating egg cytoplasm mimics the fertilization process which forms a zygote, i.e., elevated DNA synthesis. (See specification at page 7, line 37 to page 10, line 10). Polejaeva cloned pigs using a serial nuclear transfer method of first placing the somatic cell nucleus in an MII oocyte, i.e., contact with an MII oocyte cytoplasm, followed by transfer into a zygote, i.e., contact with an activating egg cytoplasm. (See Polejaeva, I.A., et al., Nature (2000) 407:86-90, courtesy copy attached in Appendix F).

Additionally, with regard to the use of cross-species extracts, it has been common practice in science for more than 20 years to employ extracts from easily obtained sources, such as HeLa cells, for gene regulation studies and rabbit reticulocytes for *in vitro* translation studies. The extracts described in the present invention have been shown to activate not only *Xenopus* nuclei but human fetal and sperm nuclei. (See specification at page 44, lines 31-33). In addition, the basic factors involved in processes such as embryonic development and differentiation have been shown to be related and cross-functional across a broad range of species. The present

application provides not only methods for testing possible extracts but list general criteria for selecting a source. (See specification at page 31, line 32 through page 34, line 12).

Applicants believe that the specification fully enables the scope of the pending claims. As such, reconsideration and withdrawal of the rejection is requested.

### CONCLUSION

If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,



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